Kindly amend the claims as follows:

2. (Amended) A method for improving the angiogenic inductive activity of a morphogenic protein selected from the group consisting of OP-2, OP-3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, COP-5, COP-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2 in a mammal by coadministering with the morphogenic protein an effective amount of a morphogenic protein stimulatory factor, wherein the amino acid sequence has angiogenic activity.

B1

6. (Twice amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein is selected from the group consisting of BMP-3, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, COP-5, COP-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2, wherein the amino acid sequence has angiogenic activity.

B2

8. (Twice amended) The method according to claim 7, wherein the monomeric species is selected from the group consisting of OP-1, BMP-5, BMP-6, BMP-8, GDF-6, GDF-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2, wherein the amino acid sequence has angiogenic activity.

B3

10. (Twice amended) The method according to claim 9, wherein the dimeric species comprises a polypeptide selected from the group consisting of OP-1, BMP-5, BMP-6, BMP-8, GDF-6, GDF-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2, wherein the amino acid sequence has angiogenic activity.

13. (Twice amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of acidic fibroblast growth factor (aFGF), basic fibroblast growth factor FGF (bFGF), transforming growth factor-β (TGF-β), transforming growth factor-α (TGF-α), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), platelet activating factor (PAF), interleukin-8 (IL-8), placental growth factor (PGF), proliferin, B61, soluble vascular cell adhesion molecule-1 (SVCAM-1), soluble E-selectin, ephrin, 12-hydorxyeicosatetraenoic acid, tat protein of HIV-1, angiogenin, prostaglandin.

14. (Twice amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of basic fibroblast growth factor (bFGF), platelet derived transforming growth factor-β1 (TGF-β1).

15. (Twice amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor is selected from the group consisting of basic fibroblast growth factor (bFGF).

16. (Twice amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor is selected from the group consisting of platelet derived transforming growth factor-β1 (TGF-β1).

REMARKS

Applicants acknowledge that the Examiner has withdrawn the enablement rejection with respect to claims 6, 8, 10 and 13-16.

In response to the Examiner's rejections and to expedite prosecution, applicants have canceled claim 5. Applicants have canceled this claim without prejudice and without waiver of their right to file for and obtain claims directed to any canceled subject matter in divisional and continuing applications which claim priority from this application.

Applicants have amended claim 2 to recite that the morphogenic protein is selected from the group consisting of OP-2, OP-3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, COP-5, COP-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2, wherein the amino acid sequence has angiogenic activity. Support for this amendment is provided, e.g., on specification page 16, line 14 to page 17, line 30.

Applicants have amended claims 6, 8 and 10 to replace the recitation of "amino acid sequence variant" with "an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID

NO: 2". Support for this amendment is provided, e.g., on specification page 17, line 16 to page 18, line 23.

Applicants have amended claims 13-16 to delete the recitation of amino acid sequence variants.

None of the amendments introduces any new matter.

Applicants now address these amendments in response to the Examiner's rejections.

35 U.S.C. § 102(b)

The Examiner has maintained the novelty rejection of claims 2, 4-6, 9-14, 16-17 and 19 under 35 U.S.C. § 102(b) in view of Duneas et al. (Growth Factors, 15, pp. 259-277 (1998))("Duneas"). The Examiner contends that Duneas teaches that hOP-1 and TGF-β1 interact synergistically to induce angiogenesis and vascular invasion. Applicants traverse.

Amended claim 2 recites a method for improving the angiogenic activity of a morphogenic protein by coadministering an effective amount of a morphogenic protein stimulatory factor. The present application teaches that the morphogenic protein itself has angiogenic activity and that the morphogenic protein stimulatory factor improves that angiogenic activity. Applicants respectfully submit that Duneas does not teach that treatment with hOP-1 alone induces any angiogenesis and that treatment with TGF-β1 improves the angiogenic effect of hOP-1. Rather, the treatment with hOP-1 alone in Duneas does not result in any angiogenic activity. In fact, figures 6A and 6C of Duneas which are photomicrographs of calvarial defects demonstrate that there is no visible vascular invasion when these defects are treated with 20 and 100 µg/ml of hOP-1, respectively. This is unlike the claims of the present application which required that the morphogenic protein has some

angiogenic activity. Therefore, claim 2 (and claims dependent thereon) is novel over Duneas. Accordingly, applicant requests that the Examiner withdraw this rejection.

35 U.S.C. § 102(e)

The Examiner has rejected claims 2-5, 7 and 12-15 under 35 U.S.C. § 102(e) in view of Goldberg et al. (US patent 6,013,624) ("Goldberg") as evidenced by Amano et al. (Arch. Oral Biol., 44, pp. 935-946 (1999)) ("Amano"). The Examiner contends that Goldberg teaches a method for improving the angiogenic inductive activity of a morphogenic protein, scatter factor, by coadministering FGF. The Examiner also contends that Amano teaches that scatter factor is osteogenic.

Applicants traverse. However, to expedite prosecution, applicants have amended claim 2 (and therefore claims dependent therefrom) to recite that the morphogenic protein is selected from the group consisting of OP-2, OP-3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, COP-5, COP-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2. As amended the claims do not recite scatter factor as a morphogenic protein. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 2-5, 7, 12-15, 17 and 19 under 35 U.S.C. § 103(a) contending that they are obvious over Goldberg as

evidenced by Amano. The Examiner contends that it would have been *prima facie* obvious to the skilled worker at the time of the invention to administer scatter factor and FGF simultaneously to a target locus because Goldberg teaches that angiogenesis can be enhanced by administering scatter factor in combination with a growth factor. Applicants traverse.

Claim 2 as amended recites a method for improving the angiogenic inductive activity of a morphogenic protein selected from the group consisting of OP-2, OP-3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, COP-5, COP-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2 by coadministering a morphogenic protein stimulatory factor.

Goldberg teaches a method of enhancing angiogenesis by administering scatter factor and FGF. Amano teaches that hepatocyte growth factor enhances bone and cartilage formation during embryonic mouse mandibular development in vitro. Neither Goldberg nor Amano recites morphogenic protein selected from the group consisting of OP-2, OP-3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, GDF-1, GDF-2, GDF-3, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, DPP, Vg-1, Vgr-1, 60A protein, NODAL, UNIVIN, SCREW, ADMP, NEURAL, COP-5, COP-7 and an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2 by coadministering a morphogenic protein stimulatory factor. Applicants respectfully submit that nothing in Goldberg or Amano, either alone or in

combination teaches the invention as recited in amended claim 2 and claims dependent therefrom. Accordingly, applicant requests that the Examiner withdraw this obviousness rejection.

35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6, 8, 10 and 13-16 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors at the time of the invention had possession of the claimed invention. The Examiner states that the written description is not commensurate in scope with the claims which read on allelic variants. The Examiner also states that the structure of naturally occurring allelic sequences are not defined nor is the structure of allelic variant proteins encoded by allelic variant genes defined. The Examiner further states that with the exception of OP-1 or bFGF, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and or encoded variants. Citing Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) ("Amgen") and University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997) ("Lilly"), the Examiner concludes that the amino acid sequence of the variants is required. Applicants traverse in part and amend in part.

First, applicants respectfully submit that the specification does not provide written description only for OP-1 and bFGF. Rather, the specification provides adequate written description for all the morphogenic proteins and morphogenic protein stimulatory factors recited in 6, 8, 10 and 13-16. The recited morphogenic proteins and stimulatory factors are well known and have been described in the art. Accordingly, applicants need

not provide in the specification a recitation of the sequence of each of the proteins recited in the claims.

Second, applicants have amended the variant recitation with respect to the morphogenic proteins to replace "amino acid sequence variants thereof" with "an amino acid sequence having at least 70% amino acid sequence homology with residues 330-431 of SEQ ID NO: 2, wherein the amino acid sequence has angiogenic activity". The specification provides an adequate description of the claimed amino acid sequences based on function and homology with residues 330-341 of SEQ ID NO: 2. Thus, unlike the situation in Amgen, the claimed amino acid sequences are defined both structurally, by sequence homology, and functionally. Further, unlike Lilly, the specification also describes the physical structure of the amino acid sequences because the claimed amino acid sequences must have at least 70% amino acid homology with residues 330-431 of SEQ ID NO: 2.

Third, applicants have canceled the recitation of amino acid variants with respect to the morphogenic protein stimulatory factors.

Accordingly, for all the above reasons, applicants request that the Examiner withdraw the written description rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance of the pending claims.